Executive Summary (4th DSRC)

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Registration No.: 32/Ph.D./DPSRU/2019 **Date of DSRC:** 29 JAN 2024

Title of thesis: Molecular Docking Studies, Synthesis and Biological Evaluation of Novel Pyrimidine Derivatives as a Potential ALK Inhibitors

Abstract:

Introduction: The ALK inhibitors have become a viable option for anticancer therapy with the availability of several FDA-approved molecules.

Objectives: Designing a synthetic scheme for the final compounds based on in-silico computational methods. Analyzing the synthesized compounds using modern analytical techniques. Evaluating the anticancer activity of the synthesized compounds.

Methodology: A pharmacophore was designed using computational studies such as docking and 3D/2D-QSAR analysis utilizing the 4MKC PDB. Intermediates containing a 2,4-diarylaminopyrimidine scaffold were utilized for the synthesis of final compounds. The progress of chemical reactions was monitored using thin-layer chromatography (TLC) to ensure reaction completion. The reaction mixture was then worked up to obtain a crude mixture, which was subsequently purified using silica gel column chromatography to isolate the desired products. The structures of all synthesized compounds were characterized using mass spectrometry and NMR analytic techniques. Biological activity of the synthesized compounds was evaluated through ALK enzyme inhibition assay and MTT assay.

Results: The biological evaluation of the synthesized compounds was conducted through the ALK enzyme inhibition assay.Among the tested compounds, KEN18 exhibited the most promising result, with an absorption reading at a concentration of 250 µM. In the cell viability assay conducted on A549 cell lines, compounds KEN7, KEN14, KEN18, KEN21, KEN23, and B1 demonstrated IC_{50} values of 77.75 µM, 117.31 µM, 42.83 µM, 123.34 µM, 113.34 µM, and 7.5 µM, respectively, compared to the standard drug crizotinib (2 µM).

Conclusions: Among the synthesized compounds, KEN 18 and B1 showed the most potent ALK inhibitory activity, with IC_{50} values of 42.83 µM and 7.5 µM, respectively. Further investigation is necessary for the development of novel ALK inhibitors targeting NSCLC using these heterocyclic compounds.

Outcomes of the work:

- The standardized experimental procedure for the Suzuki reaction and reductive amination will be helpful for the researchers working in organic synthesis.
- The potent compounds can be utilized to design the pharmacophore for novel ALK inhibitors.
- Future research on our synthesized compounds could potentially contribute to the development of more effective ALK inhibitors against NSCLC.